CERTIFICATE OF MAILING UNDER 37 C F R § 1.8

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John V Hanley, Reg No. 38,161

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of

Inventor: Johnston William McAvoy
and Coral Gwenda Chamberlain

Serial No. 08/648,092

Filed: May 17, 1996

For: A METHOD FOR PREVENTING OR CONTROLLING CATARACT

Examiner: Z. Fay

Group Art Unit: 1614

Client ID/Matter No. UNSYD-39709

June 14, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. SECTION 1.132

I, Antony Wilks Burgess, declare as follows:

1. I was one of ordinary skill in the art at the time of the present invention. More specifically, I have been working in the field of growth factors and their actions on cells since 1976. I am currently the Director of the Ludwig Institute for Cancer Research in Melbourne, Australia. I have held this position since 1980. I also hold the positions of Professor of Cell Biology in the Department of Surgery at the University of Melbourne and an Honorary

Principal Research Fellow at The Walter and Eliza Hall Institute of Medical Research. Attached hereto and marked "**Exhibit A**" is a copy of my Curriculum Vitae.

2. This Declaration is made in support of a concurrently filed Amendment in the above-identified application, the Amendment being in response to the Office Action dated December 19, 2005.

3. Before November 19, 1993, I had extensive experience with, and published numerous papers on, growth factors, receptors, intracellular pathways, growth factor antagonists and inhibitors Before November 19, 1993, I supervised staff whose research focused on the TGF-β system. Since 1990, I have held the position of Editor-in-Chief of the journal "Growth Factors". I was elected a Fellow of the Australian Academy of Science in 1993 as an established expert in growth factors, and was involved in the inauguration of the Co-operative Research Centre for Cellular Growth Factors in Melbourne, Australia, in 1993.

4. On or before November 19, 1993, I would have understood the term "inhibitors of TGF-β" to mean compounds (eg. small molecular entities (chemicals) or biologicals) which interfere with the action of TGF-β in such a way so as to inhibit the biological activity of TGF-β That is, I would have understood the term "inhibitor of TGF-β" to refer to any compound that inhibits the biological activity of TGF-β. On or before November 19, 1993, it was known by persons of ordinary skill in the art such as myself that the biological activity of TGF-β may be inhibited by various means by inhibitors of TGF-β. For example, the inhibitors of TGF-β may have bound to and sequestered TGF-β, competed with TGF-β binding to its cell surface receptors, reduced the amount of TGF-β by inhibiting the synthesis of TGF-β, or in some other

way prevented TGF-β from inducing biological effects that typically result from the binding of TGF-β to its cell surface receptors.

5. On or before November 19, 1993, the structure of TGF-β and its receptors were described in the art. On or before November 19, 1993, there were several assays for TGF-β described in the art, including assays where TGF-β had an inhibitory effect on cellular proliferation. These assays often involved epithelial cells (eg. mink lung epithelial cells or African green monkey kidney (BSC-1) epithelial cells) or hemopoietic cells (eg. myeloid or lymphoid). TGF-β inhibitors would prevent TGF-β interfering with the proliferation of these cell lines. On or before November 19, 1993, a person of ordinary skill in the art could have readily established, without undue experimentation, whether a particular compound was an inhibitor of TGF-β using such bioassays.

6. An example of a common bioassay for TGF-β used on or before November 19, 1993 utilized mink lung epithelial cells. When TGF-β is added to mink lung cell cultures under appropriate conditions, the rate of cell proliferation is suppressed. A test compound was considered an inhibitor of TGF-β if the test compound reduced the suppressive effect of TGF-β on mink lung cell proliferation. On or before November 19, 1993, a person of ordinary skill in the art could have readily established, without undue experimentation, whether a particular compound was an inhibitor of TGF-β using this assay. The assay utilizing mink lung epithelial cells is described in various documents, including Lucas C, Fendly BM, Mukku VR, Wong WL, Palladino MA, "Generation of Antibodies and Assays for Transforming Growth Factor β", *Methods in Enzymology*, 198: 303-316 (1991), and Danielpour D, Sporn MB, "Differential Inhibition of Transforming Growth Factor β1 and β2 Activity by α_2-Macroglobulin", *The Journal of Biological Chemistry*, 265 (12): 6973-6977 (1990).

Attached hereto and marked "**Exhibit B**" is a copy of Lucas C, Fendly BM, Mukku VR, Wong WL, Palladino MA, *Methods in Enzymology*, 198: 303-316 (1991). Attached hereto and marked "**Exhibit C**" is a copy of Danielpour D, Sporn MB, *The Journal of Biological Chemistry*, 265 (12): 6973-6977 (1990).

7. An example of another bioassay for TGF-β used on or before November 19, 1993 utilized African green monkey kidney epithelial (BSC-1) cells. When TGF-β is added to African green monkey kidney epithelial (BSC-1) cell cultures under appropriate conditions, the rate of cell proliferation is suppressed. A test compound was considered an inhibitor of TGF-β if the test compound reduced the suppressive effect of TGF-β on African green monkey kidney epithelial (BSC-1) cell proliferation. On or before November 19, 1993, a person of ordinary skill in the art could have readily established, without undue experimentation, whether a particular compound was an inhibitor of TGF-β using this assay. The assay utilizing African green monkey kidney epithelial (BSC-1) cells is described in the art, eg. McPherson JM, Sawamura SJ, Ogawa Y, Dineley K, Carrillo P, Piez KA, "The Growth Inhibitor of African Green Monkey (BSC-1) Cells Is Transforming Growth Factors β1 and β2", *Biochemistry*, 28: 3442-3447 (1989). Attached hereto and marked "**Exhibit D**" is a copy of McPherson JM, Sawamura SJ, Ogawa Y, Dineley K, Carrillo P, Piez KA, *Biochemistry*, 28: 3442-3447 (1989).

8. On or before November 19, 1993, a person of ordinary skill in the art of growth factor research could prepare and culture lens epithelial explants. The preparation and culture of lens epithelial explants are described in the art, eg. McAvoy JW, Fernon VTP, "Neural retinas promote cell division and fibre differentiation in lens epithelial explants", *Curr Eye Res.*

3: 827-834 (1984). Attached hereto and marked **"Exhibit E"** is a copy of McAvoy JW, Fernon VTP, *Curr Eye Res*. 3: 827-834 (1984).

9. On or before November 19, 1993, a person of ordinary skill in the art of growth factor research, having the benefit of reviewing the specification for the present application, could have obtained commercially natural TGF-β (or could have produced and purified either natural or recombinant TGF-β by methods known and described in the art), and used this material to induce changes in lens cells growing as explants. Such a person of ordinary skill in the art could have readily confirmed that a particular inhibitor of TGF-β inhibits the TGF-β-induced changes to lens cells by a lens explant study such as that described in the Examples in the specification Further, such a person of ordinary skill in the art could have readily measured the effects of TGF-β-induced changes in lens cells and could, therefore, have used similar measurements to test the effects of other TGF-β inhibitors on TGF-β–induced cataract-like or after-cataract-like changes in lens cells.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATE: June 14, 2006

Antony W Burgess

ANTONY WILKS BURGESS

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